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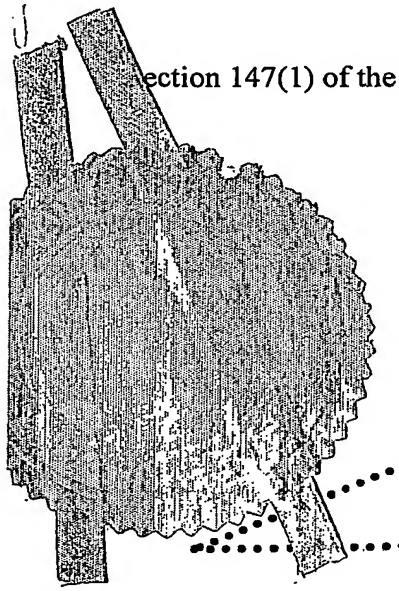
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

REC'D 30 SEP 2004
WIPO PCT

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 03/04/2003 in respect of Patent Application No.333/MUM/2003 of SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI- KURLA ROAD, ANDHERI (E), MUMBAI – 400 059, MAHARASHTRA, INDIA, AN INDIAN COMPANY.

This certificate is issued under the powers vested in me under section 147(1) of the Patents Act,1970.



PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Dated this 30th day of August 2004.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA

AN INDIAN COMPANY

hereby declare -

(i) that we are in possession of an invention titled **"PROGRAMMED DRUG DELIVERY SYSTEM".**

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

Dr. Dharmadhikari, Nitin Bhalachandra; Dr. Zala, Yashoraj Rupsinh
of SUN PHARMACEUTICAL ADVANCED RESEARCH CENTRE LIMITED, Bombay College of Pharmacy Building, 2nd Floor, C.S.T. Road, Kalina, Mumbai 400098, Maharashtra, INDIA; all Indian nationals.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-28397632, FACSIMILE NO- 28212010.

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333/MUM/2003
3/4/2003

3/4/03
2786

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 2nd day of April 2003.

(Signatures) 1. _____
Dr. Dharmadhikari, Nitin Bhalachandra

2. _____
Dr. Zala, Yashoraj Rupsinh

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

1) Provisional specification (3 copies)
2) Fee Rs. 5000 in cheque bearing No. 415284 dated 13/02/2003 on ICICI Bank Limited.

We request that a patent may be granted to us for the said invention

Dated this 2nd day of April 2003.

(Signature) .....
SUDHIR VALIA
DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To
The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

PROGRAMMED DRUG DELIVERY SYSTEM

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification describes the nature of this invention.

PROGRAMMED DRUG DELIVERY SYSTEM

The present invention relates to a programmed drug delivery system for delivery of a beneficial agent. The versatile and novel drug delivery system is useful for programmed delayed, controlled, spaced or targeted drug delivery. More particularly, the programmed drug delivery system is useful for targeted drug delivery to a specific site in the gastrointestinal tract, at which site the beneficial agent may be delivered as a pulse, or in a rate controlled manner.

BACKGROUND OF THE INVENTION

Oral administration of a drug provides a plasma level time profile of a drug or its active or inactive metabolite, which can be modulated by the design of the drug delivery system or dosage form. Drug delivery systems releasing the drug slowly over longer duration have been traditionally used to improve therapy by

- improving patient compliance to dosage regimens through the decrease in the number of doses the patient has to take in a day, by providing desired effective plasma levels for therapeutic efficacy over the duration of therapy for example throughout the day including at night when the patient is asleep;
- decreasing peak plasma levels when they are associated with side effects;
- reducing side effects in chronic therapy by reducing the fluctuation in plasma levels seen after multiple dosing of conventional release systems;
- when the drug has local action on the gastrointestinal mucosa, to spread the release spatially over the whole of the gastrointestinal mucosa as the drug delivery system is transported in the mucosa by the motility of the gastrointestinal tract.

The drawbacks associated with this mode of delivery are -

- Some drugs are absorbed preferentially from a particular region of the gastrointestinal tract.
- Some drugs may develop tolerance, i.e. when delivered such that when constant plasma levels are maintained, a decline in pharmacologic response at the constant plasma level of drug is seen. In such instances higher levels are required at a later time.
- Drug delivery is not designed according to the chronopharmacokinetics and chronopharmacology of the patient. For example, therapy may optimally require different

plasma levels at different times of the day, whereas these systems are not designed to provide such modulated delivery.

For some drugs the maintenance of constant plasma levels over a long duration is unnecessary for therapeutic efficacy. For example, once a peak plasma level is achieved, the desired therapeutic drug action is initiated and persists even if plasma levels decline. In such instance, it is undesirable to maintain the drug plasma levels at the constant higher levels. However, for such drugs there is a need for providing drug delivery systems which will pack multiple doses in a once-daily unit dosage form and deliver each dose at the dosing time as a pulse.

Another traditional mode of release is delayed release utilizing enteric coated dosage form. Enteric coated dosage forms (i.e. dosage forms coated with a polymer having a pH dependent solubility such that it does not dissolve in the gastric fluids but dissolves in the intestinal fluids) have been traditionally used to prevent the release of drug in the stomach and to instead release the drug in the small intestine when -

- the drug is unstable in the acidic gastric fluid or undergoes enzymatic degradation in the fluid, or as it passes the gastric mucosa
- the drug causes irritation to the gastric mucosa
- prolonged duration of drug delivery is desired, which can be given by delivering an initial drug amount from uncoated elements in the dosage form, and delivering the remaining part in the small intestine by enteric coated elements of the dosage form
- targeted release of the drug to the small intestine or to the colon is desired
- spacing between delivery of a part of the dose immediately in the stomach, and the rest of the dose is desired.

The drawback associated with using enteric coated systems is that the time of emptying of the enteric coated system from the stomach into the small intestine is highly variable and dependent on a variety of physiological factors such as presence or absence of food in the stomach, the type and calories of the food, the physiology of the patient with respect to the gastrointestinal motility and pattern, and the size of the enteric coated unit. Thus, the delay, prolongation, spacing or targeting of drug delivery is not predictably programmed.

It is an object of the present invention to provide a programmed drug delivery system that is versatile and its various embodiments are suitably designed -

- in a first embodiment to deliver a beneficial agent after a programmed predictable delay, which delay is independent of gastric emptying time; this delivery or release being referred to herein as timed release.
- in a second embodiment to deliver a beneficial agent after a delay, which delay is dependent on gastric emptying time; this delivery or release being to referred to herein as delayed release.
- in a third embodiment to deliver a beneficial agent immediately and after a programmed predictable delay period to provide a time-programmed pulsatile plasma level time profile over short to prolonged durations, which plasma level time profile and the spaced pulses therein are in turn independent of gastric emptying time; this delivery or release being referred to herein as programmed pulsatile delivery.
- in a fourth embodiment to deliver a beneficial agent immediately on administration and immediately after delay periods, which delay periods are dependent on gastric emptying time, to provide a pulsatile plasma level time profile over short to prolonged durations, which plasma level time profile and the spaced pulses therein are in turn dependent on gastric emptying time; this delivery or release being referred to herein as pulsatile delivery.
- in a fifth embodiment to deliver a beneficial agent immediately on administration and in a controlled manner after delay periods that are independent of gastric emptying time to provide a controlled plasma level time profile over short to prolonged durations, which plasma level time profile and the spaced pulses therein are in turn independent of gastric emptying time; this delivery or release being referred to herein as time-programmed controlled release.
- in a sixth embodiment to deliver a beneficial agent immediately on administration, and in a controlled manner after delay periods that are dependent on gastric emptying time to provide a controlled plasma level time profile over short to prolonged durations, which plasma level time profile and the spaced pulses therein are in turn dependent on gastric emptying time; this delivery or release being referred to herein as controlled release.
- in an seventh embodiment to deliver a first beneficial agent immediately on administration and to deliver a second beneficial agent immediately after a delay period that is independent of gastric emptying time, to provide spaced pulse delivery of the two beneficial agents, wherein the spacing of the two different beneficial agents is independent of gastric emptying time; this delivery or release being referred to herein as programmed-spaced delivery or release.

- in a eighth embodiment to deliver a first beneficial agent immediately on administration and to deliver a second beneficial agent immediately after a delay period that is dependent on gastric emptying time, to provide spaced pulse delivery of the two beneficial agents, wherein the spacing of delivery of the two different beneficial agents is dependent on gastric emptying time; this delivery or release being referred to herein as spaced delivery or release.
- in a ninth embodiment to deliver one or more beneficial agents to a target site in the gastrointestinal tract, for example in the upper small intestine or the large intestine, particularly the right colon, where the delivery is a pulse or immediate delivery; this delivery or release being referred to herein as targeted pulse delivery.
- in a tenth embodiment to deliver one or more beneficial agents to a target site in the gastrointestinal tract, for example in the upper small intestine or the large intestine, particularly the right colon, in a rate controlled manner; this delivery or release being referred to herein as targeted controlled release.

The present invention provides a programmed drug delivery system comprising :

(a) a core composition comprising one or more beneficial agents and pharmaceutically acceptable excipients, wherein at least one excipient swells to at least twice its volume when exposed to an aqueous environment,

(b) a water insoluble coat surrounding the core composition, wherein the coat is impermeable to the beneficial agent and other core components, but may be permeable or impermeable to water,

(c) an orifice in the coat connecting the interior of the delivery system to the exterior environment,

(d) a polymer composition applied so as to cover the orifice wherein the polymer composition comprises a polymer selected from the group consisting of water soluble polymer, water swellable polymer, pH-dependent polymer and a mixture thereof, and

(e) optionally, an immediate release composition comprising the same or different beneficial agent.

Figure 1 provides a diagrammatic representation of a "central-band-type" programmed drug delivery system of the present invention, comprising a core with beneficial agent and excipients covered by a coat, with the passageway being blocked with a polymer composition. The

passageway is present in the center of the system, with the polymer composition being present as a band.

Figure 2 provides a diagrammatic representation of a "off-centered-band-type" programmed drug delivery system of the present invention, comprising a core with beneficial agent and excipients covered by a coat, with the passageway being blocked with a polymer composition. The passageway is off-centered and the polymer composition is present as a band.

Figure 3 provides a diagrammatic representation of a "band-on-edge-type" programmed drug delivery system of the present invention, comprising a core with beneficial agent and excipients covered by a coat, with the passageway being blocked with a polymer composition. The passageway is present on the edge of the system and the polymer composition is present as a band.

Figure 4 provides a diagrammatic representation of a "central-plug-type" programmed drug delivery system of the present invention, comprising a core with beneficial agent and excipients covered by a coat, with the passageway being blocked with a polymer composition. The passageway is present in the center, with the polymer composition being present as a plug.

Figure 5 provides a diagrammatic representation of a "off-centered-plug-type" programmed drug delivery system of the present invention, comprising a core with beneficial agent and excipients covered by a coat, with the passageway being blocked with a polymer composition. The passageway is off-centered and the polymer composition is present as a plug.

Figure 6 provides a diagrammatic representation of a "plug-on-edge-type" programmed drug delivery system of the present invention, comprising a core with beneficial agent and excipients covered by a coat, with the passageway being blocked with a polymer composition. The passageway is present on the edge of the system and the polymer composition is present as a plug.

The present invention provides a programmed drug delivery system comprising a core composition comprising one or more beneficial agents and pharmaceutically acceptable excipients, wherein at least one excipient swells to at least twice its volume when exposed to an aqueous environment, a water insoluble coat surrounding the core composition, wherein the coat

is impermeable to the beneficial agent and other core components, but may be permeable or impermeable to water, an orifice in the coat connecting the interior of the delivery system to the exterior environment, and a polymer composition applied so as to cover the orifice, wherein the polymer composition comprises a polymer selected from the group consisting of pH-independent water soluble or swellable polymer, water insoluble polymer, pH-dependent polymer and mixtures thereof, and optionally, an immediate release composition comprising the same or different beneficial agent. The core of the programmed drug delivery system of the present invention may be suitably designed to affect a programmed delayed, controlled, spaced or targeted delivery, with a pulsed or controlled release of the one or more beneficial agents.

The programmed drug delivery system of the present invention is useful in providing improved drug delivery. Drugs that may be used in the programmed drug delivery system of the present invention may be selected from the following, viz. alcohol abuse preparations, drugs used for Alzheimer's disease, anesthetics, acromegaly agents, analgesics, antiasthmatics, anticancer agents, anticoagulants and antithrombotic agents, anticonvulsants, antidiabetics antiemetics, antiglaucoma, antihistamines, anti-infective agents, antiparkinsons, antiplatelet agents, antirheumatic agents, antispasmodics and anticholinergic agents, antitussives, carbonic anhydrase inhibitors, cardiovascular agents, cholinesterase inhibitors, treatment of CNS disorders, CNS stimulants, contraceptives, cystic fibrosis management, dopamine receptor agonists, endometriosis management, erectile dysfunction therapy, fertility agents, gastrointestinal agents, immunomodulators and immunosuppressives, memory enhancers, migraine preparations, muscle relaxants, nucleoside analogues, osteoporosis management, parasympathomimetics, prostaglandins, psychotherapeutic agents, sedatives, hypnotics and tranquilizers, drugs used for skin ailments, steroids and hormones

Examples of alcohol abuse preparations are chlorazepate, chlordiazepoxide, diazepam, disulfiram, hydroxyzine, naltrexone and their salts.

Examples of analgesics are acetaminophen, aspirin, bupivacain, buprenorphine, butorphanol, celecoxib, clofenadol, choline, clonidine, codeine, diflunisal, dihydrocodeine, dihydroergotamine, dihydromorphine, ethylmorphine, etodolac, eletriptan, eptazocine, ergotamine, fentanyl, fentoprofen, hyaluronic acid, hydrocodon, hydromorphon, hylan, ibuprofen, lindomethacin, ketorolac, ketotifen, levomethadon, levallorphan, levorphanol, lidocaine, mefenamic acid, meloxicam, meperidine, methadone, morphine, nabumetone, nalbuphin, nefopam, nalorphine,

naloxone, naltrexone, naproxen, naratriptan, nefazodone, mormethadon, oxaprozin, oxycodone, oxymorphon, pentazocin, pethidine, phenpyramid, piritramid, piroxicam, propoxyphene, refecoxib, rizatriptan, salsalaketoprofen, sulindac, sumatriptan, tebacon, tilidin, tolmetin, tramadol, zolmitriptan and their salts.

Examples of antiasthmatics are ablukast, azelastine, bunaprolast, cinalukast, cromitrile, cromolyn, enofelast, isamoxole, ketotifen, levcromekalin, lodoxamide, montelukast, ontazolast, oxarbazole, oxatomide, piriprost potassium, pirolate, pobilukast edamine, quazolast, repirinast, ritolukast, sulukast, tetrazolastmeglumine, tiaramide, tibenelast, tomelukast, tranilast, verlukast, verofylline, zarirlukast.

Examples of anticancer agents are adriamycin, aldesleukin, allopurinol, altretamine, amifostine, anastrozole, asparaginase, betamethasone, bexarotene, bicalutamide, bleomycin, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, conjugated estrogen, cortisone, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, dactinomycin, denileukin, dexamethasone, discodermolide, docetaxel, doxorubicin, eloposidem, epirubicin, epoetin, epothilones, estramustine, esterified estrogen, ethinyl estradiol, etoposide, exemestane, flavopirdol, fluconazole, fludarabine, fluorouracil, flutamide, floxuridine, gemcitabine, gemtuzumab, goserelin, hexamethylmelamine, hydrocortisone, hydroxyurea, idarubicin, ifosfamide, interferon, irinotecan, lemiposide, letrozole, leuprolide, levamisole, levothyroxine, lomustine, mechlorethamine, melphalan, mercaptopurine mechlorethamine, megesterol, methotrexate, methylprednisolone, methyltestosterone, mithramycin, mitomycin, mitotane, mitoxantrone, mitozolomide, mutamycin, nilutamide, paclitaxel, pamidronate, pegaspargase, pentostatin, plicamycin, porfimer, prednisolone, procarbazine, rituximab, sargramostim, semustine, streptozocin, tamoxifien, temozolamide, teniposide, testolactone, thioguanine, thiotepa, tomudex, topotecan, toremifene, trastumuzab, tretinoin, semustine, streptozolocin, valrubicin, verteprofin, vinblastine, vincristine, vindesine, vinorelbine and their salts.

Examples of anticoagulants and antithrombic agents are warfarin, dalteparin, heparin, tinzaparin, enoxaparin, danaparoid, abciximab, alprostadil, altiplase, anagralide, anistreplase, argatroban, ataprost, beraprost, camonagreel, cilostazol, clinprost, clopidogrel, cloricromen, dermatan, desirudin, domitroban, drotaverine, epoprostenol, eptifibatide, fradafiban, gabexate, iloprost, isbogrel, lamifiban, lamoteplase, lefradafiban, lepirudin, levosimendan, lexipafant, melagatran, nafagrel, nafamostsat, nizofenone, orbifiban, ozagrel, pamicogrel, parnaparin, quinobendan,

reteplase, sarpogralate, satigrel, silteplase, simendan, ticlopidine, vapiprost, tirofiban, xemilofiban, Y20811 and their salts.

Examples of anticonvulsants are carbamazepine, clonazepam, clorazepine, diazepam, divalproex, ethosuximide, ethotion, felbamate, fosphenytoin, gabapentin, lamotrigine, levetiracetam, lorazepam, mephenytoin, mephobarbital, metharbital, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide, and their salts.

Examples of antidiabetic agents are acarbose, acetohexamide, carbutamide, chlorpropamide, epalrestat, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepid, glyburide, glyhexamide, metformin, miglitol, nateglinide, orlistat, phenbutamide, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide, tolcyclamide,tolrestat, troglitazone, voglibose and their salts.

Examples of antiemetics are alprazolam benzquinamide, benztropine, betahistine, chlorpromazine, dexamethasone, difenidol, dimenhydrinate, diphenhydramine, dolasetron, domperidone, dronabinol, droperidol, granisetron, haloperidol, lorazepam, meclizine, methylprednisolone, metoclopramide, ondansetron, perphenazine, prochlorperazine, promethazine, scopolamine, tributine, triethylperazine, triflupromazine, trimethobenzamide, tropisetron and their salts.

Examples of antiglaucoma agents are alprenoxime, dapiprazole, dipivefrin, latanoprost, naboctate, pirnabine and their salts.

Examples of antihistamines are acrivastine, activastine, albuterol, azelastine, bitolterol, alimemazine, amlexanox, azelastine, benzydamine, brompheniramine, cetirizine, chlorpheniramine, cimetidine, clemastine, cycloheptazine, cyproheptadine, diclofenac, diphenhydramine, dotarizine, ephedrine, epinastine, epinephrine, ethylnorepinephrine, fenpoterol, fexofenadine, flurbiprofen, hydroxyzine, ibuprofen, isoetharine, isoproterenol, ipratropium bromide, ketorolac, levocetirizine, loratidine, mequitazine, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, promethazine, pseudoephedrine, pyrilamine, salmeterol, terbutaline, tranilast, xanthine derivatives, xylometazoline and their salts.

Examples of anti-infective agents are abacavir, albendazole, amantadine, amphotericin, amikacin, aminosalicylic acid, amoxycillin, ampicillin, amprenavir, atovaquin, azithromycin, aztreonam, carbenicillin, cefaclor, cefadroxil, cefamandole, cefazolin, cefdinir, cefepime, cefexime, cefoperazone, cefotaxime, cefotitam, cefoperazone, cefoxitin, cefpodoxine, cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cephalexin, chloroquine, cidofovir, cilastatin, ciprofloxacin, clarithromycin, clavulinic acid, clindamycin, colistimethate, dalfopristine, dapsone, daunorubicin, delavirdin, demeclocycline, didanosine, doxycycline, doxorubicin, efavirenz, enoxacin, erythromycin, ethambutol, ethionamide, famsiclovir, fluconazole, flucytocin, foscarnet, fosfomycin, ganciclovir, gatifloxacin, griseofulvin, hydroxychloroquine, imipenem, indinavir, interferon, isoniazide, itraconazole, ivermectin, ketoconazole, lamivudine, levofloxacin, linezolide, lomefloxacin, lovacarbef, mebendazole, mefloquine, meropenem, methanamine, metronidazole, minocycline, moxefloxacin, nalidixic acid, nelfinavir, neomycin, nevirapine, nitrofurantoin, norfloxacin, ofloxacin, olseltamnivir, oxytetracycline, palivizumab, penicillins, perfloxacin, piperacillin, praziquantel, pyrazinamide, pyrimethamine, quinidine, quinupristine, retonavir, ribavirin, rifabutine, rifampicin, rimantadine, saquinavir, sparfloxacin, stavudine, streptomycin, sulfamethoxazole, teramycin, terbinafine, tetracycline, ticarcillin, thiabendazole, tobramycin, trimethoprim, trimetraxate, troleandomycin, trovafloxacin, valacyclovir, vancomycin, zalcitabine, zanamivir, zidovudine and their salts.

Examples of antiparkinsons are amantadine, adrogolide, altinicline, benztropine, biperiden, brasofensine, bromocriptine, budipine, cabergoline, CHF-1301, dihydrexidine, entacapone, etilevodopa, idazoxan, iometopane, lazabemide, melevodopa, carbidopa/levodopa, mofegiline, moxiraprine, pergolide, pramipexole, quinelorane, rasagiline, ropinirole, seligiline, talipexole, tolcapone, trihexyphenidyl and their salts.

Examples of antirheumatic agents are azathiprine, betamethasone, celecoxib, cyclosporin, diclofenac, hydroxychloroquine, indomethacin, infliximab, mercaptobutanedioic acid, methylprednisolone, naproxen, penicillamine, piroxicam, prednisolone, sulfasalazine and their salts.

Examples of platelet agents are abciximab, anagrelide, aspirin, cilostazol, clopidogrel, dipyridamole, epoprostenol, eptifibatide, ticlopidine, tinofiban and their salts.

Examples of antispasmodics and anticholinergic agents are aspirin, atropine, diclofenac, hyoscyamine, mesoprostol, methocarbamol, phenobarbital, scopolamine and their salts.

Examples of antitussives are acetaminophen, acrivastin, albuterol, benzonatate, beractant, brompheniramine, caffeine, calfactant, carbetapentane, chlorpheniramine, codeine, colfuscerin, dextromethorphan, dornase alpha, doxylamine, epinephrine, fexofenadine, guaiphenesin, ipratropium, levalbuterol, metaproterenol, montelukast, pentoxyphyline, phenylephrine, phenylpropanolamine, pirbuterol, poractant alpha, pseudoephedrine, pyrilamine, salbuterol, salmeterol, terbutaline, theophylline, zafirlukast, zileuton and their salts.

Examples of carbonic anhydrase inhibitors are acetazolamide, dichlorphenamide, dorzolamide, methazolamide, sezolamide and their salts.

Examples of cardiovascular agents are abciximab, acebutolol, activase, adenosine, adrenaline, amidarone, amiloride, amlodipine, amyl nitrate, atenolol, atorvastatin, benazepril, bepiridil, betaxalol, bisoprolol, candesartan, captopril, cartenolol, carvedilol, cerivastatin, chlorthalidone, chlorthiazole, clofibrate, clonidine, colestipol, colosevelam, digoxin, diltiazem, disopyramide, dobutamine, dofetilide, doxazosin, enalapril, epoprostenol, eprosartan, esmolol, ethacrynate, erythrityl, felodipine, fenoidapam, fosinopril, fleicainide, flurosemide, fluvastatin, gemfibrozil, hydrochlorthiazide, hydroflumethazine, ibutilide, indapamide, isosorbide, irbesartan, labetolol, lacidipine, lisinopril, losartan, lovastatin, mecamylamine, metoprolol, metaraminol, metazolone, methylchlorthiazide, methyldopa, metyrosine, mexiletine, midrodine, milrinone, moexipril, nadolol, niacin, nicardipine, nicorandil, nifedipine, nimodipine, nisoldipine, nitroglycerin, phenoxybenzamine, perindopril, polythiazide, pravastatin, prazosin, procainamide, propafenone, propranolol, quanfacine, quinapril, quinidine, ranipril, reteplase, simvastatin, sotalol, spironolactone, streptokinase, telmisartan, terazosin, timolol, tocainamide, torsemide, trandolapril, triamterene, trapidil, valsartan and their salts.

Examples of cholinesterase inhibitors are donepezil, edrophonium, neostigmine, pyridostigmine, rivastigmine, tacrine and their salts.

Examples of CNS stimulants are caffeine, doxapram, dexoamphetamine, donepezil, edrophonium, methamphetamine, methylphenidate, modafinil, neostigmine, pemoline, phentermine, pyridostigmine, rivastigmine, tacrin and their salts.

Examples of cystic fibrosis management are dornase alpha, pancrelipase, tobramycin and their salts.

Examples of dopamine receptor agonists are amantadine, cabergoline, fenoldopam, pergolide, pramipexil, ropinirole and their salts.

Examples of drugs used for endometriosis management are danazol, goserelin, leuprolide, nafarelin, norethindrone and their salts..

Examples of drugs used for erectile dysfunction therapy are alprostadil, sildenafil, yohimbine and their salts.

Examples of gastrointestinal agents are aldosetron, bisacodyl, bismuth subsalicylate, celecoxib, difoxin, dipheoxylate, docusate, famotidine, glycopyrrolate, infliximab, lansoprazole, loperamide, metaclopramide, nizatidine, omeprazole, pantoprazole, rabeprazole, ranitidine, simethicone, sucralfate, and their salts.

Examples of immunomodulators and immunosupressives are azathioprin, ceftizoxine, cyclosporin, daclizumab, glatiramer, immunoglobulin, interferon, leflunomide, levamisol, mycophenolate, mausomanab, phthalidomide, ribavirin, sirolimus and their salts.

Examples of drugs used in alzheimer's disease are CP 118954, donepezil, galanthamine, metrifonate, rivastigmine, tacrine, TAK-147 and their salts.

Examples of drugs used for migraine preparations are acetaminophen, dihydroergotamine, divalproex, ergotamine, propranolol, risatriptan, sumatriptan, trimetrexate and their salts.

Examples of muscle relaxants are alcuronium-chloride, azapropazon, atracurium, baclofen, carisoprodol, quinine derivatives, chloromezanon, chlorophenesincarbamate, chlorozoxazon, cyclobenzaprine, dantrolene, decamethoniumbromide, dimethyltubocurariniumchloride, doxacurium, fenyramidol, gallamintriethiodide, guaiphenesin, hexafluoreniumbromide, hexacarbacholinbromide, memantin, mephenesin, meprobamate, metamisol, metaxalone, methocarbamol, mivacurium, orphenadrin, pancuronium, phenazon, phenprobamate,

pipecuronium, rapacuronium, rocuronium, succinylcholine, suxamethoniumchloride, tetrazepam, tizanidine, tubocurarine chloride, tybamate, vecuronium and their salts.

Examples of nucleoside analogues are abacavir, acyclovir, didanosine, ganciclovir, gemcitabine, lamivudine, ribavirin, stavudine, zalcitabine and their salts.

Examples of drugs used for osteoporosis management are alendronate, calcitonin, estradiol, estropipate, medroxyprogesterone, norethindrone, norgestimate, pamidronate, raloxifen, risdronate, zolendronate and their salts.

Examples of parasympathomimetics are bethanechol, biperidine, edrophonium, glycopyrolate, hyoscyamine, pilocarpine, tacrine, yohimbine and their salts.

Examples of prostaglandins are alprostadil, epoprostenol, misoprostol and their salts.

Examples of psychotherapeutic agents are acetophenazine, alentemol, alpertine, alprazolam, amitriptyline, aripiprazole, azaperone, batelapine, befipiride, benperidol, benzindopyrine, bimithil, biriperone, brofoxine; bromperidol; bromperidol, bupropion, buspirone, butaclamol, butaperazine; butaperazin, carphenazine, carvotroline, cericlamine, chlorazepine, chlordiazepoxide, chlorpromazine; chlorprothixene, cinperene, cintriamide, citalopram, clomacran, clonazepam, clopenthixol, clopimozide, clopipazan, cloroperone, clothiapine, clothixamide, clozapine; cyclophenazine, dapiprazole, dapoxetine, desipramine, divalproex, dipyridamole, doxepin, droperidol, duloxetine, eltoprazine, eptipirone, etazolate, fenimide, flibanserin, flucindole, flumezapine, fluoxetine, fluphenazine, fluspiperone, fluspirilene, flutroline, fluvoxamine, gepirone, gevotroline, halopemide, haloperidol, hydroxyzine, hydroxynortriptyline, iloperidone, imidoline, lamotrigine, loxapine, enperone, mazapertine, mephobarbital, meprobamate, mesoridazine, mesoridazine, milnacipran, mirtazapine, metiapine, milenperone, milipertine, molindone, nafadotride, naranol, nefazodone, neflumozide, ocaperidone, odapipam, olanzapine, oxethiazine, oxiperomide, pagoclone, paliperidone, paroxitene, penfluridol, pentiapine perphenazine, phenelzine, pimozide, pinoxepin, pipamperone, piperacetazine, pipotiazine, piquindone, pirlindole, pivagabine, pramipexole, prochlorperazine, prochlorperazine, promazine, quetiapine, reboxetine, remoxipride, remoxipride, risperidone, rimcazole, robolzotan, selegiline, seperidol, sertraline, sertindole; seteptiline, setoperone, spiperone, sunipitron, tepirindole, thioridazine, thiothixene, tiapride, tioperidone, tiospirone,

topiramate, tranylcypromine, trifluoperazine, trifluperidol, triflupromazine, triflupromazine, trimipramine, venlafaxine, ziprasidone and their salts.

Examples of sedatives, hypnotics and tranquilisers are bromazepam, buspirone, clazolam, clobazam, chlorazepate, diazepam, demoxepam, dexmedetomitine, diphenyhydramine, doxylamine, enciprazine, estrazolam, hydroxyzine, ketazolam, lorazatone, lorazepam, loxapine, medazepam, meperidine, methobarbital, midazolam, nabilone, nisobamate, oxazepam, pentobarbital, promethazine, propofol, triazolam, zaleplon, zolpidem and their salts.

Examples of drugs used for treatment of skin ailments are acitretin, alclometasone, allitretinoin, betamethasone, calciprotrine, chlorhexidine, clobetasol, clocortolone, clotriamozole, collagenase, cyclosporin, desonide, difluorosone, doxepine, eflornithine, finasteride, fluocinolone, flurandrenolide, fluticasone, halobetasol, hydrochloroquine, hydroquinone, hydroxyzine, ketoconazole, mafenide, malathion, menobenzone, neostigmine, nystatin, podofilox, povidone, tazorotene, tretinoin and their salts.

Examples of steroids and hormones are alclometasone, betamethasone, calcitonin, citrorelix, clobetasol, clocortolone, cortisones, danazol, desmopressin, desonide, desogestrel, desoximetasone, dexamethasone, diflorasone, estradiol, estrogens, estropipate, ethynlestradiol, fluocinolone, flurandrenolide, fluticasone, glucagon, gonadotropin, goserelin, halobetasol, hydrocortisone, leuprolide, levonorgestrel, levothyroxine, medroxyprogesterone, menotropins, methylprednisolone, methyltestosterone, mometasone, naferelin, norditropin, norethindrone, norgestrel, octreolide, oxandrolone, oxymetholone, polytropin, prednicarbate, prednisolone, progesterone, sermorelin, somatropin, stanozolol, testosterone, urofollitropin and their salts.

An embodiment of the programmed drug delivery system of the present invention is particularly useful for agents that are susceptible to the gastric environment such as proton pump inhibitors like pantoprazole, omeprazole, lansoprazole, esomeprazole, rabeprazole, pariprazole, leminoprazole, or an enantiomer, isomer, derivative, free base or salt thereof; lipid-lowering agents such as lovastatin, pravastatin, atorvastatin, simvastatin; agents that are targeted to the intestine for local action such as 5-aminosalicylic acid, corticosteroids such as beclomethasone, budesonide, fluticasone, tixocortol useful in treating Crohn's disease and ulcerative colitis; agents that may be inactivated by the gastric contents such as enzymes like pancreatin, antibiotics such as erythromycin; agents that cause bleeding or irritation of the gastric mucosa such as aspirin,

steroids, non-steroidal anti-inflammatory compounds like ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, oxaprozin, diflunisal, diclofenac, indomethacin, tolmetin, sulindac, etodolac, acetaminophen, platelet inhibitors such as abciximab, intergrelin, dipyridamole; nucleoside analogs such as didanosine, transfer factor preparations, hormones, insulin, and other agents that have decreased stability in the gastric environment, as well as agents that are required for local action in the latter part of the gastrointestinal tract. The agents may be used as their base or as their pharmaceutically acceptable salt or solvate thereof.

The core of the programmed drug delivery system of the present invention may include one or more excipients that are capable of swelling upon exposure to an aqueous environment, and may be selected from hydrophilic non-polymeric compounds and from hydrophilic polymers. The hydrophilic polymers may be of plant, animal, mineral or synthetic origin. The swelling agent may be selected from (A) cellulose derivatives such as C_{1-4} alkyl celluloses like methyl cellulose and ethyl cellulose; hydroxy C_{1-4} alkyl celluloses such as hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and the like; hydroxy C_{1-4} alkyl C_{1-4} alkyl celluloses such as hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose and the like; carboxy C_{1-4} alkyl celluloses such as carboxymethyl cellulose, carboxyethyl cellulose, and their alkali salts; and the like, (B) vinylpyrrolidone polymers such as polyvinyl pyrrolidone, crosslinked polyvinyl pyrrolidone or crospovidone and the like, (C) copolymers of vinyl pyrrolidone and vinyl acetate, (D) gums of plant, animal, mineral or synthetic origin such as (i) agar, alginates, carrageenan, furcellaran obtained from marine sources, (ii) guar gum, gum Arabic, gum tragacanth, karaya gum, locust bean gum obtained from terrestrial plants, (iii) microbial polysaccharides such as dextran, gellan gum, rhamsan gum, welan gum, xanthan gum, and (iv) synthetic or semi-synthetic gums such as propylene glycol alginate, hydroxypropyl guar and modified starches like sodium starch glycolate. The swelling agent used in the present invention may be a combination of the agents mentioned above. Preferably, a combination of two agents is used to provide a controlled swelling thereby causing the coat or core to rupture or burst open at a predetermined time after oral administration of the delivery system.

The core of the programmed drug delivery system of the present invention may include pharmaceutically acceptable excipients such as binders, diluents, lubricants, water soluble compounds for inducing osmosis, wicking agents and the like.

In one embodiment, the core comprises a first composition comprising one or more beneficial agents, and optionally other pharmaceutically acceptable excipients, and a second composition comprising water soluble compounds for inducing osmosis, and one or more excipients that swell upon imbibing water. Preferably, the first and the second composition are arranged as bilayers, but they may also be admixed with each other. A passageway is formed on the coated core on the side comprising the layer with osmosis-inducing compounds, and it is blocked by a polymer composition that erodes or dissolves at a predetermined time, or upon reaching the latter portion of the gastrointestinal tract. The fluid from the surrounding environment enters the coated core due to osmosis either through the water insoluble coating or the passageway or both, thereby causing the swellable component of the first layer to swell. The pressure exerted by the swollen excipients causes a fracture to develop usually at the passageway and the coat ruptures or bursts, thereby causing opening of the tablets and subsequent release the beneficial agents.

The coat surrounding the core is such that it does not release substantial amount of the drug, until it ruptures or bursts at a predetermined time after oral administration of the delivery system, or at a specific location in the gastrointestinal tract. The coating agents that may be used in the present invention are selected from among water insoluble polymers and hydrophobic compounds known to a person skilled in the art, such that the coat is insoluble in an aqueous environment. The coat is impermeable to the beneficial agent and other core components, but may be permeable or impermeable to water. When it is permeable to water, the core imbibes water from the external environment and swells. When it is impermeable to water, the core absorbs water through the passageway when the polymer composition covering the passageway is eroded or dissolved.

A passageway in the form of an orifice is formed in the coat by suitable means such as mechanical or laser drilling. The orifice may be present in the center of the coated core, may be off-centered or may be present on the edge of the coated core.

The orifice is blocked with a polymer composition, applied such that the beneficial agent is not released until the polymer erodes or dissolves. The polymers that may be used to block the passageway may be pH-independent water soluble polymers and water swellable polymers, or may be pH-dependent polymers, or mixtures thereof. These include, but are not limited to, cellulose and cellulose derivatives such as methyl cellulose, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, methacrylic acid and methacrylate esters such as anionic and cationic polymers of methacrylic acid,

copolymers of methacrylates, copolymers of acrylates and methacrylates, copolymers of ethacrylate and methylmethacrylate, and mixtures thereof. The polymer composition may block the orifice by forming a band over the orifice or it may plug the orifice. The polymer composition blocks the orifice to provide a release of the one or more beneficial agents from the core at a predetermined time and/or location in the gastrointestinal tract after oral administration. Embodiments that use pH-independent polymers provide release at a predetermined time and those that use pH-dependent polymer provide release at a specific location in the gastrointestinal tract.

The programmed drug delivery system of the present invention may optionally include an immediate release composition comprising the same or different beneficial agent. The immediate release composition may be in the form of granules, pellets, beads, tablets that release the beneficial agent immediately upon oral administration, or it may be present in the form of an immediate release coat or layer partially or wholly covering the programmed drug delivery system.

Delayed release :

One embodiment of the present invention provides a programmed drug delivery system for delayed delivery of the beneficial agent, in the form of a tablet comprising a core comprising one or more beneficial agents, one or more pharmaceutical excipients that swell upon exposure to aqueous medium, and optionally other pharmaceutically acceptable excipients, wherein the core is coated with a water insoluble and water impermeable coating. Aqueous latex dispersions may be used for the purpose and thus the use of organic solvents may be avoided. A passageway is drilled in the coated core, the passageway being blocked with an enteric polymer in the form of a band or a plug. The delay of release in this embodiment is dependent on the gastric emptying time because an enteric polymer is used. When the enteric polymer is applied so as to form a band covering the orifice, then contact between the enteric polymer composition or the enteric band formed thereof and the core is avoided. This is ideally suited for systems where the core is alkaline in nature. For example, drugs from the category of proton-pump inhibitors such as omeprazole, pantoprazole, lansoprazole, esomeprazole and rabeprazole are unstable in an acidic environment and thus are formulated with alkaline excipients, or the drug is used in the form of its alkaline salt for the purpose of achieving the desired stability. An enteric coating over such a composition has two undesirable effects – (a) it tends to dissolve rapidly because of the alkaline milieu of the core, thus releasing the drug in the acidic gastric fluids, defeating the purpose of

providing the enteric coat to protect the drug from the acidic gastric fluids, and (b) the acidic enteric coat decreases the pH at the surface of the core, thus decreasing the stability of the drug in that region. Thus, in prior art compositions a subcoat of water soluble or water dispersible excipients is applied. The present invention provides a novel method of total separation of the core from the enteric polymer band by the water insoluble and drug impermeable coat over the core. The impermeable coating does not allow release of the core components in the early portion of the gastrointestinal tract. The pH-dependent polymer composition in the form of a plug or a band blocking the orifice dissolves or erodes upon reaching higher pH environment in the intestine. Water is imbibed by the core through the orifice and the coating when the coating is permeable to water, or through the orifice when the coat is impermeable to water. The swellable component of the core thus swells and exerts a pressure on the coat. A fracture is initiated usually at the orifice, thereby causing the coat to rupture or burst, thereby causing opening of the tablet and subsequent release of the core components in a conventional manner.

Timed release :

Another embodiment of the present invention provides a programmed drug delivery system that delivers the beneficial agent after a predictable delay, the delay being independent of gastric emptying time, in the form of a tablet comprising a core comprising one or more beneficial agents, one or more pharmaceutical excipients that swell upon exposure to aqueous medium, and optionally other pharmaceutically acceptable excipients, wherein the core is coated with a water insoluble coating. A passageway is drilled in the coat and is covered with a band or a plug of a polymer composition that is soluble or swellable in the gastrointestinal fluids and whose water solubility is pH-independent. Upon erosion or dissolution of the soluble polymer the passageway is exposed and the fluid from the surrounding enters the system, causing it to swell and exert a pressure on the coat. The coat then ruptures to release the contents of the core in a conventional manner. Alternatively, the core may be coated with a polymer composition that is insoluble but permeable to water, and the passageway may be coated with a water-insoluble pH-independent polymer. The water entering the core through the permeable membrane causes the core to swell and the swelling exerts a pressure on the coat. However, the insoluble coating covering the passageway is unaffected by the fluid and the swelling pressure generated inside the system leads to development of a weak point in the coat at the junction of the insoluble coat and the permeable polymer. Hence, the coat ruptures and releases the beneficial agent to the surrounding in a conventional manner.

Pulsatile delivery :

In yet another embodiment the programmed drug delivery system of the present invention provides an immediate delivery of a beneficial agent, followed by a delayed delivery of the same agent, the delay being dependent on gastric emptying time. The system provides a pulsatile plasma level time profile with spaced pulses of the beneficial agent that are dependent on gastric emptying time. At least one delayed release portion is present in the form of a core comprising the beneficial agent, one or more pharmaceutical excipients that swell upon exposure to aqueous medium, and optionally other pharmaceutically acceptable excipients, wherein the core is coated with a water insoluble and water impermeable coating. A passageway is drilled in the coated core and it is blocked with an enteric polymer in the form of a band or a plug. The beneficial agent is released from the core after a delay in a conventional manner, the delay being dependent on gastric emptying time, i.e. after the system reaches the intestine. The immediate release portion may be present in the form of granules, pellets, beads, or tablets, or it may be present as an immediate release coat covering at least a part or whole of the delayed release portion. Alternatively, the immediate release portion may be provided by mixing it with the water insoluble, water impermeable polymer, and using the mixture thus obtained to coat the delayed release core. The system may have more than one delayed release portions, the delayed release portions utilising polymer compositions covering the orifice wherein the polymer used in each delayed release portion dissolves at different pH. Thus, pulsatile release may be provided.

Programmed pulsatile delivery :

Yet another embodiment of the present invention provides a programmed drug delivery system that provides an immediate release of a beneficial agent and a delayed release of the same agent, the delay being independent of gastric emptying time, which release is referred to herein as timed release. The system provides a time-programmed pulsatile plasma level time profile, with spaced pulses of the agent that are independent of the gastric emptying time. At least one timed release portion is present in the form of a core comprising a beneficial agent, one or more pharmaceutical excipients that swell upon exposure to aqueous medium, and optionally other pharmaceutically acceptable excipients, wherein the core is coated with a water insoluble and water impermeable coating. A passageway is drilled in the coat and is covered with a band or a plug of a polymer composition that is soluble or swellable in the gastrointestinal fluids. The beneficial agent is released from the core after a delay in a conventional manner. The immediate release portion may be present in the form of granules, pellets, beads, or tablets, or it may be present as an immediate release coat covering at least a part or whole of the delayed release portion.

Alternatively, the immediate release portion may be provided by mixing it with the water insoluble, water impermeable polymer, and using the mixture thus obtained to coat the delayed release core. The system may have more than one timed release portion to provide a pulsatile release, such that pulses of drug are released at times best suited for therapy.

Controlled release :

One embodiment of the present invention provides a programmed drug delivery system that provides an immediate release of the beneficial agent, followed by a delayed controlled release of the same agent, the delay being dependent on gastric emptying time. The delayed release portion comprises a core comprising the beneficial agent, one or more pharmaceutical excipients that swell upon exposure to aqueous medium, and optionally one or more pharmaceutically acceptable excipients, the core being surrounded by a coat comprising a polymer composition comprising water insoluble and water impermeable component. A passageway drilled in the wall is covered by a band or a plug of an enteric polymer composition. The enteric polymer erodes or dissolves upon reaching the intestine, thereby exposing the passageway. The fluid from the surrounding environment then enters the system through the passageway and causes swelling of the core and subsequent rupture of the coat. The components of the core and their quantity are selected such that the core delivers the agent in a controlled manner upon rupture of the coat in the intestine. The immediate release portion may be present in the form of granules, pellets, beads, or tablets, or it may be present as an immediate release coat covering at least a part or whole of the delayed release portion. This embodiment uses an immediate release component of a beneficial agent and a delayed controlled release component of the same beneficial agent.

Time-programmed controlled release :

Another embodiment of the present invention comprises a programmed drug delivery system that provides an immediate release of a beneficial agent, followed by a timed controlled release, the delay being independent of gastric emptying time. The delayed release portion of the system comprises a core comprising one or more beneficial agents, one or more pharmaceutical excipients that swell upon exposure to aqueous medium, and optionally other pharmaceutically acceptable excipients, wherein the core is coated with a water insoluble and water impermeable coating. A passageway is drilled in the coat and is covered with a band or a plug of a polymer composition that is soluble in the gastrointestinal fluids. Upon erosion or dissolution of the soluble polymer the passageway is exposed and the fluid from the surrounding enters the system, causing it to swell and exert a pressure on the coat. The coat then ruptures to release the contents

of the core in a rate controlled manner. The immediate release portion may be present in the form of granules, pellets, beads, or tablets, or it may be present as an immediate release coat covering at least a part or whole of the delayed release portion. This embodiment uses an immediate release component of a beneficial agent and timed controlled release component of the same beneficial agent.

Spaced delivery :

Another embodiment of the present invention provides a programmed drug delivery system that provides release of a beneficial agent immediately upon oral administration, followed by delayed release of another beneficial agent in a conventional manner, the delay being dependent on gastric emptying time. This embodiment uses an immediate release component of a beneficial agent and a delayed release component of a different beneficial agent.

Programmed spaced delivery :

Yet another embodiment of the present invention provides a programmed drug delivery system that provides an immediate release of a beneficial agent upon oral administration, followed by a delayed release of another beneficial agent, the delay being independent of gastric emptying time. This embodiment uses an immediate release component of a beneficial agent and a timed release component of a different beneficial agent.

Targeted pulse delivery :

One embodiment of the present invention provides a programmed drug delivery system providing a pulse or immediate delivery of one or more beneficial agents to a targeted site, for example in the upper small intestine or the right colon.

Targeted controlled release delivery :

Yet another embodiment of the present invention provides a programmed drug delivery system that provides targeted delivery of one or more beneficial agents, for example in the upper small intestine or the right colon, in a rate controlled manner.

The following examples merely illustrate the present invention and do not limit the scope of the invention.

Example 1

The programmed drug delivery system of the present invention was obtained in the form of tablets, wherein lactose was substituted for the drug. The dummy tablets were obtained as mentioned in Table 1 below –

Table 1

Ingredients	Quantity (% w/w)
Microcrystalline cellulose (Avicel PH 101)	56.0
Crosslinked polyvinylpyrrolidone (Crospovidone)	15.0
Meglumine	16.6
Lactose anhydrous (Pharmatose DCL –21)	6.66
Colloidal silicon dioxide (Aerosil)	3.0
Magnesium stearate	1.66
Talc	1.0
Ethyl cellulose N-10	Used as a 5% w/w solution for coating the tablet core
Diethyl phthalate	
Eudragit L-100-55	Quantity dependent on weight gain desired

Microcrystalline cellulose, crospovidone and meglumine were mixed thoroughly and granulated using purified water. The granules were mixed with lactose, colloidal silicon dioxide, magnesium stearate and talc. The mixture thus obtained was compressed using conventional means. The compressed tablets were coated with a 5% coating solution of ethyl cellulose and diethyl phthalate in dichloromethane and methanol, to a weight gain of 3.5%. An orifice was then drilled in the coated tablet, and the orifice was finally covered with a band comprising Eudragit L-100-55 as the enteric polymer, and diethyl phthalate as plasticiser. The amount of weight gain of the tablet after coating with the enteric polymer was varied to achieve different time of opening in pH 6.8 buffer.

The tablets were evaluated for opening time study and were introduced in pH 6.8 buffer. Tablets that were not drilled, as well as drilled tablets not covered by an enteric band were also introduced in pH 6.8 buffer for comparison. Five tablets of each type were included for the study. The observations are recorded in Table 2 below.

Table 2

Tablet no.	Tablet description	Opening time in pH 6.8 buffer
1	Undrilled	1 hour 10 minutes
2	Undrilled	1 hour 10 minutes
3	Undrilled	1 hour 20 minutes
4	Undrilled	Not for 2 hours
5	Undrilled	Not for 2 hours
6	Drilled	20 minutes
7	Drilled	20 minutes
8	Drilled	20 minutes
9	Drilled	25 minutes
10	Drilled	25 minutes
11	Enteric banded	25 minutes (0.9% weight gain)
12	Enteric banded	30 minutes (0.9% weight gain)
13	Enteric banded	35 minutes (1.25% weight gain)
14	Enteric banded	35 minutes (1.27% weight gain)
15	Enteric banded	1 hour (1.9% weight gain)

As is apparent from the table above, the opening time is predictable and reliable for enteric banded tablets. An increase in weight gain after coating with the enteric polymer results in an increase in opening time of the tablet.

Example 2

The programmed drug delivery system of the present invention may be obtained in the form of tablets as mentioned in Table 3 below. The lactose anhydrous used as per Table 2 above may be below may be substituted by any drug. In this example it was substituted by Esomeprazole magnesium.

Table 3

Ingredients	Quantity (% w/w)
Microcrystalline cellulose (Avicel PH 101)	56.0
Crosslinked polyvinylpyrrolidone (Crospovidone)	15.0
Meglumine	16.66
Esomeprazole magnesium	6.66
Colloidal silicon dioxide (Aerosil)	3.0
Magnesium stearate	1.66
Talc	1.0
Ethyl cellulose N-10	Used as a 5% w/w solution for coating the tablet core
Eudragit L-100-55	

The tablet core was obtained as mentioned in Example 1 above. The compressed cores were coated with a 5% w/w solution of ethyl cellulose and Eudragit L-100-55 in dichloromethane and ethanol, to a weight gain of 6% and 7% in a fluid bed coater.

The tablets were evaluated for opening time study in 0.1N hydrochloric acid and pH 6.8 buffer. Five tablets were used for the study. The observations are recorded in Table 4 below.

Table 4

Tablets used for the study	Opening time	
	0.1N HCl	pH 6.8 buffer
Tablets comprising esomeprazole magnesium as the drug, coated to a weight gain of 6% by weight of the core	None of the tablets opened for 2 hours	28-30 minutes

The above example demonstrates a programmed drug delivery system for drugs, which system does not release the beneficial agent in the early portion of the gastrointestinal tract, i.e. there is no release for 2 hours after oral administration. However, the drug is released within 28-30 minutes in pH 6.8 buffer indicating that the system is capable of delivering the drug in the latter portion of the gastrointestinal tract in a reliable manner. The core of the system may be suitably designed to affect a conventional, sustained, controlled or pulsed release of the beneficial agent.

Example 3

The programmed drug delivery system of the present invention may be obtained in the form of tablets as mentioned in Table 5 below.

Table 5

Ingredients	Quantity (%w/w)
Omeprazole (micronised)	9.09
Silicified microcrystalline cellulose (Prosolv SMCC 90®)	75.86
Sodium lauryl sulfate	1.0
Polyethylene glycol (PEG 4000)	1.0
Meglumine	4.5
Crosslinked polyvinyl pyrrolidone (Crospovidone)	8.0
Magnesium stearate	0.5
Ethyl cellulose standard 10 P	Used as a 5%w/w solution
Diethyl phthalate	5% w/w of ethyl cellulose
Hydroxypropyl methylcellulose phthalate (HPMCP-50)	Used as a 5%w/w solution
Diethyl phthalate	10%w/w of HPMCP-50

Omeprazole, sodium lauryl sulfate, PEG 4000 and meglumine were mixed together and passed through ASTM (American Society of Testing and Materials) #40 sieve. The mixture thus obtained was mixed with Prosolv and crospovidone to obtain a blend. This blend was lubricated with magnesium stearate and compressed to obtain the core. The core was coated with a solution

of ethyl cellulose and diethyl phthalate in a mixture of dichloromethane-methanol (4:1) to a weight gain of from about 14% to about 15% by weight of the core. An orifice was drilled in the coated core and this orifice was coated with a solution of HPMCP-50 and diethyl phthalate in a mixture of dichloromethane-methanol (3:1).

The programmed drug delivery system thus obtained was subjected to tablet opening time studies using United States Pharmacopoeia type II dissolution apparatus at 37°C, at a speed of 75 rpm. The medium used was 900ml of 0.1N HCl for the first two hours, followed by pH 6.8 buffer for one hour. None of the tablets opened in 0.1N HCl for two hours, while all the tablets opened within 9 minutes and 23 minutes in pH 6.8 buffer. The average opening time in pH 6.8 buffer was 18 minutes.

Example 4

The programmed drug delivery system of the present invention may be obtained in the form of tablets as mentioned in Table 6 below.

Table 6

Ingredients	Quantity (%w/w)
Omeprazole (micronised)	9.09
Silicified microcrystalline cellulose (Prosolv SMCC 90®)	75.86
Sodium lauryl sulfate	1.0
Polyethylene glycol (PEG 4000)	1.0
Disodium hydrogen phosphate, anhydrous	0.91
Crosslinked polyvinyl pyrrolidone (Crospovidone)	8.0
Magnesium stearate	0.5
Lactitol monohydrate	3.6
Ethyl cellulose standard 10 P	Used as a 5%w/w solution
Diethyl phthalate	5% w/w of ethyl cellulose
Hydroxypropyl methylcellulose phthalate (HPMCP-50)	Used as a 5%w/w solution
Diethyl phthalate	10%w/w of HPMCP-50

Omeprazole, sodium lauryl sulfate, PEG 4000 and anhydrous disodium hydrogen phosphate were mixed together and passed through ASTM (American Society of Testing and Materials) #40 sieve. The mixture thus obtained was mixed with Prosolv, lactitol monohydrate and crospovidone to obtain a blend. This blend was lubricated with magnesium stearate and compressed to obtain the core. The core was coated with a solution of ethyl cellulose and diethyl phthalate in a mixture of dichloromethane-methanol (4:1) to a weight gain of from about 14% to about 15% by weight of the core. An orifice was drilled in the coated core and this orifice was coated with a solution of HPMCP-50 and diethyl phthalate in a mixture of dichloromethane-methanol (3:1).

The programmed drug delivery system thus obtained was subjected to tablet opening time studies using United States Pharmacopoeia type II dissolution apparatus at 37°C, at a speed of 75 rpm. The medium used was 900ml of 0.1N HCl for the first two hours, followed by pH 6.8 buffer for one hour. None of the tablets opened in 0.1N HCl for two hours, while all the tablets opened within 9 minutes and 23 minutes in pH 6.8 buffer. The average opening time in pH 6.8 buffer was 18 minutes.

Dated this 2nd day of April, 2003.

SUDHIR VALIA,
DIRECTOR,
SUN PHARMACEUTICAL INDUSTRIES LIMITED.

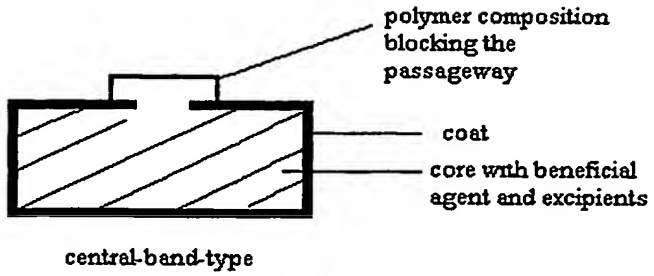

Figure 1

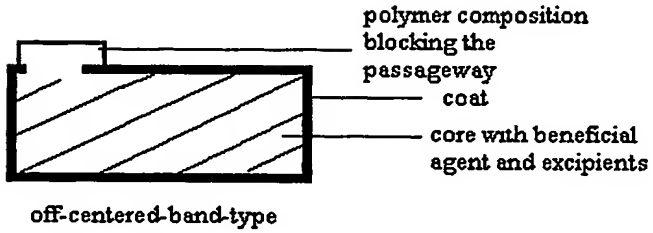

Figure 2

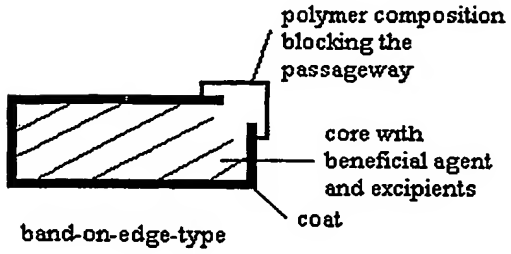

Figure 3

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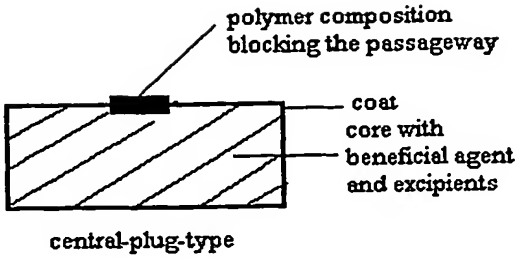

Figure 4

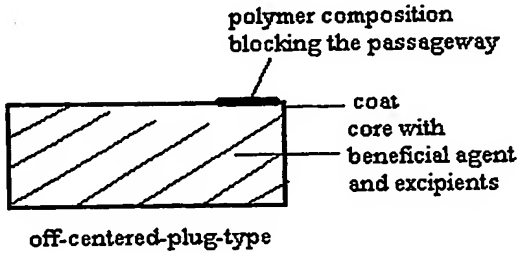

Figure 5

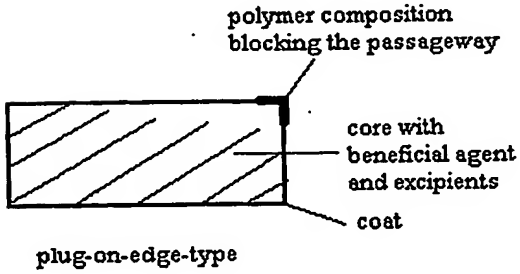

Figure 6

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